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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,365	02/13/2002	Yeckezkel Barenholz	BARENHOLTZ-1A	5480

1444 7590 03/05/2004

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,365	BARENHOLZ ET AL.	
	Examiner	Art Unit	
	Gollamudi S Kishore, PhD	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment dated 12-4-03 is acknowledged.

Claims included in the prosecution are 50-89.

Claim Rejections - 35 USC ' 112

1.The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 50-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to how one can obtain a suspension and not a solution when the carotenoid (which is lipophilic) is added to a solution of a phospholipid in an organic solvent as recited in the amended claim 50.

Claims 68-74 recite 'effective amounts'; this term has no meaning if the disease to be treated is not recited in the claims.

Claim Rejections - 35 USC ' 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 61-78, 80 and 81-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Meybeck (5,034,228) of record.

Meybeck discloses topical liposomal formulations containing beta-carotene for dermatological and cosmetic applications. The applications include 'to fight aging' and protection against sun (protection against free-radicals, singlet oxygen). The compositions can also be administered orally. The method of preparation of liposomes disclosed by Meybeck is similar to instant method. The method involves dissolving the phospholipid and the carotenoid in an organic solvent and removing the solvent to prepare a dry preparation, hydrating the powder with an aqueous medium and lyophilizing the liposomes and hydrating them again when needed. Although there is no explicit teaching in Meybeck that the liposome forming lipids in the organic solvent is to a level close to saturation, the amounts of the phospholipid used by Meybeck as seen from examples are more than the amounts noted in instant specification and therefore, deemed to be close to saturation. (Abstract, col. 3, lines 19-46; Examples 1 and 17, and claims). Applicant's amendment to make the above claims as dependent on the process claim is noted. However, since the product by process claims are still the product claims and applicant has not met the burden of showing that the prior art product is patentably distinct from instant product, the rejection is made on the product claims.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that as appreciated by those versed in the art, retinoids and specifically tretinoins are polar substances, and as such are water-immiscible. This

argument is not found to be persuasive since tretinoin is a homologue of 13-cis retinoic acid and as far as the examiner is aware of retinoic acid is water insoluble compound. The examiner requests any evidence to show to show that these compounds are water-soluble. Irrespective of this issue, the examiner points out that Meybeck's teachings are for tretinoin and carotenoids (alpha, beta, delta and gamma carotenes (see claim 5 and Example 17 of Meybeck).

5. Claims 61-82 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 94/13265 (Smith) of record.

WO discloses liposomal formulations containing beta-carotene for prevention of oxidation damage caused by singlet oxygen and other reactive oxygen species. The liposomes are made from phospholipids including egg phosphatidylcholine. The mode of administration is either topical or oral (capsules or tablets) (abstract, pages 4-6, 9-11, Examples and claims).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Smith discloses dissolving phospholipids or other liposome forming compounds in a solvent and the solution is placed into a suitable reaction vessel and the antioxidants are then dissolved in an aqueous solution. According to applicant since the carotenoids used in the present invention are water-immiscible, they cannot possibly be dissolved in an aqueous solution. Applicant is incorrect in making this statement. According to Example B on page 8 of Smith, the lipid and the antioxidants (lipophilic antioxidants) are dissolved in an organic solvent mixture.

6. Claims 61-78 and 80-82 are rejected under 35 U.S.C. 102(b) as being anticipated by Stahl (FEBS Letters, 427, 1998).

Stahl discloses liposomal formulations containing carotenoid mixtures. The carotenoids include lycopene, lutein, and beta-carotene. According to Stahl, mixtures of carotenoids are more effective than the single compounds (note the abstract, Materials and Methods and Tables). The intended use has no significance in composition claims.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the method of preparation is different. However, as pointed out above, instant claims are product claims and applicant has not demonstrated that the product is patentably distinct from the prior art product. With regard to applicant's arguments based on MLV's containing lycopene, the examiner points out that instant claims just recite liposomes and not either MLVs or SUVs. The rationale behind arguments based on the instability when stored for three weeks with soy oil covering them is not readily apparent to the examiner since liposomes are generally in form of aqueous suspensions and carotenoids being lipophilic and are entrapped in the lipid bilayer one would expect them to dissolve in soy oil covering them.

Claim Rejections - 35 USC ' 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 50-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meybeck cited above.

The teachings of Meybeck have been discussed above. In essence, Meybeck discloses topical liposomal formulations containing beta-carotene for dermatological and cosmetic applications. The applications include, 'fighting aging' and 'protection against sun' (protection against free-radicals, singlet oxygen). The compositions can also be administered orally (abstract, col. 3, lines 19-46; Examples 1 and 17, and claims). The method of preparation of liposomes disclosed by Meybeck is similar to instant method. The method involves dissolving the phospholipid and the carotenoid in an organic solvent and removing the solvent to prepare a dry preparation (as opposed to instant steps where the lipid is first dissolved in the organic solvent and then carotenoid is added to this solution), hydrating the powder with an aqueous medium and lyophilizing the liposomes and hydrating them again when needed. Although there is no explicit teaching in Meybeck that the liposome forming lipids in the organic solvent is to a level close to saturation, as pointed out above, the amounts of the phospholipid used by Meybeck as seen from examples are more than the amounts noted in instant specification. Assuming that they are different, it is deemed obvious to one of ordinary skill in the art to manipulate the amounts of the phospholipid since the phospholipid amounts determine how many liposomes are formed and how much of the lipophilic carotenoids are incorporated in the lipid bilayers. Meybeck does not teach cyclohexane

as the organic solvent. However, the purpose the solvent is to dissolve the phospholipid, it is deemed obvious to one of ordinary skill in the art to select a suitable solvent as long as it serves the desired purpose. Meybeck does not teach a kit. However, it is deemed obvious to one of ordinary skill in the art to supply the components in the form of a kit so that the artisan can obtain fresh preparations of liposomes when needed.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant once again argues that Meybeck et al dissolve (disclose) loading of retinoids and since these are polar substances one reading Meybeck would not be able to encapsulate carotenoids in liposomes using this method. These arguments have been addressed above. Furthermore, contrary to applicant's arguments in Meybeck et al, both lecithin and the retinoid are dissolved in an organic solvent (dichloromethane) and then hydrated. Since both lecithin, retinoid and carotenoid are lipophilic it is the examiner's position that whether they are added to the organic solvent together or lecithin first dissolved in the organic solvent and then the retinoid or carotenoid is added to this solution, the result would be the same, that is, formation of a solution of lipid and the carotenoid and applicant has not shown otherwise.

9. Claim 55 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meybeck cited above, further in view of Mackaness (4,192,859).

The teachings of Meybeck have been discussed above. What is lacking in Meybeck is the use of cyclohexane as the solvent in the preparation of liposomes.

The use of cyclohexane would have been obvious to one of ordinary skill in the art, with the expectation of obtain at least similar results, since Mackaness teaches that organic solvents such as cyclohexane and chloroform could be used in dissolving the phospholipids in the preparation of liposomes (col. 3, lines 40-45).

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that even though Mackaness discloses hexane (cyclohexane) as the solvent to dissolve phospholipids, combining Mackaness with Meybeck et al would still not lead to the present invention since Meybeck et al dissolve their retinoids in water to form liposomes. The examiner once again points out that applicant is incorrect in stating so since Meybeck does not dissolve the retinoid in water, but dissolves both lecithin and the retinoid in dichloromethane which is an organic solvent.

10. Claims 50-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meybeck or WO 94/13265 cited above, further in view of Stahl cited above.

The teachings of Meybeck and WO 94 have been discussed above. What are lacking in these references are the teachings of the use of a combination of carotenoids or the use of lycopene.

Stahl as discussed above, discloses liposomal formulations containing carotenoid mixtures. The carotenoids include lycopene, lutein, and beta-carotene. According to Stahl, lycopene is the most effective compound and the mixtures of carotenoids are more effective than the single compounds (note the abstract, Materials and Methods and Tables).

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S Kishore, PhD whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman K Page can be reached on (571) 272-0602. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gollamudi S Kishore, PhD
Primary Examiner
Art Unit 1615

GSK

The use of lycopene as the carotenoid in Meybeck or WO would have been obvious to one of ordinary skill in the art since according to Stahl, lycopene is more effective than other carotenoids. The use of mixtures of carotenoids would have been obvious to one of ordinary skill in the art since Stahl teaches that mixtures of carotenoids are more effective than the single compounds.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the cited publications teach away from the method of the instant invention since they either teach loading of the carotenoid into liposomes either by dissolving both components together in a suitable solvent as suggested by Meybeck et al or Stahl et al or by dissolving the carotenoid in a suitable solvent and only then adding thereto the dried lipids, as suggested by Smith and Mackaness et al. These arguments are not found to be persuasive. First of all, Stahl is combined for its teachings of the superiority of lycopene and the effectiveness of the combination of carotenoids. Secondly, as pointed out above, since both lecithin, retinoid and carotenoid are lipophilic it is the examiner's position that whether they are added to the organic solvent together or lecithin first dissolved in the organic solvent and then the retinoid or carotenoid is added to this solution, the result would be the same, that is, formation of a solution of lipid and the carotenoid and applicant has not shown otherwise.

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP